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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/972,743	10/05/2001	John A Flygare	018781-001823US	5345

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EXAMINER	
RAO, DEEPAK R	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 10/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/972,743	FLYGARE ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,11,18,41,43,44,54-62,95,96,98-109 and 111* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,11,18,41,43,44,54-62,95,96,98-109 and 111* is/are rejected.

7)☒ Claim(s) *3* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the amendment filed on September 20, 2005.

The amendment filed on September 20, 2005 has been entered. The rejections of the previous office action are withdrawn in view of the amendment.

Upon reconsideration, the finality of the previous office action is withdrawn, in view of following grounds of rejection, some of which were inadvertently omitted in the previous office actions of September 10, 2004 and April 8, 2005.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 43-44, 56, 58-60, 96, 99, 101 and 103-107 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a disease characterized by high low density lipoprotein particles or cholesterol levels in the blood selected from atherosclerosis, pancreatitis, and hyperlipoproteinemia, does not reasonably provide enablement for a method of treating a disease characterized by high low density lipoprotein particles or cholesterol levels in the blood generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The

nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant claims recite 'a method of treating a disease state characterized by abnormally high low density lipoprotein particles or cholesterol levels in the blood...' and the specification fails to enable one skilled in the art for the recited use. The claims cover "diseases" that are known to exist and those, that are yet to be discovered and therefore, the use of the term is extremely broad. Some of the 'diseases' associated with the mechanism stated in the claims include the following:

- Atherosclerosis. The gradual build-up of cholesterol-rich plaque on the inner wall of a large artery, which causes them to narrow and harden. Atherosclerosis is a leading cause and indicator of potential coronary artery disease.
- Hyperlipidemia. High blood levels of cholesterol and triglycerides.
- Hyperlipoproteinemia. High blood levels of lipoproteins.
- Cirrhosis. Widespread disruption in normal liver function often caused by a chronic condition such as alcoholism or hepatitis.
- Hypothyroidism. A deficiency in thyroid gland activity marked by lowered metabolism and decreased energy levels.
- Nephrotic syndrome. A grouping of symptoms that include protein in urine, low blood protein and swelling (edema). This syndrome often produces an increase in cholesterol levels.
- Uncontrolled diabetes. A metabolic condition in which blood sugar levels are high because the body cannot adequately produce or use insulin – a hormone produced in the pancreas.
- Bile-duct obstruction.
- Pancreatitis. Inflammation or infection of the pancreas.

- Some types of liver problems. A rise in lipid levels may signal biliary obstruction, cholestatic jaundice or certain other liver problems.

The specification does not provide any guidance regarding how to identify the subject 'in need of the claimed method of treatment' or 'susceptible to the disease'. Test procedure for measuring the instantly claimed compounds' ability to increase LDL receptor expression in Hep G2 cells are provided in Example 71. There is nothing in the disclosure regarding how this data correlates to the treatment of the various disorders of the instant claims. The data provided in insufficient such that no reasonable extrapolation could be made by one skilled in the art regarding the activity of the compounds. The area of receptor interactions is highly structure specific and unpredictable. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. Regarding hypercholesterolemia, Vega et al. (PubMed Abstract enclosed) state that "Hypercholesterolemia is a well-established risk factor for coronary heart disease. However, the mechanisms underlying hypercholesterolemia, elevated low density lipoprotein (LDL) in particular, are not well understood".

Further, there is no disclosure regarding how 'the subject in need of' the treatment is identified and further, how types of coronary artery diseases, liver problems, diabetes, etc. are treated. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area, and the inhibitory data provided is insufficient for one of ordinary skill in the art in order to extrapolate to all types of disorders of the claims. It is inconceivable as to how

the claimed compounds can treat the extremely difficult diseases embraced by the instant claims.

Elevated serum cholesterol levels are associated with a high risk of heart disease and 'hear diseases' embrace a vast array of problems, many of which are contradictory to others. Thus, it covers hypertension and hypotension. It covers various types of arrhythmias; angina pectoris', the thrombotic symptoms of diabetes, atherosclerosis and hyperlipoproteinaemias, ischemic heart disease including congestive heart failure and myocardial infarction, stroke, and peripheral vascular disorders, such as deep-vein thrombosis and thrombophlebitis percutaneous transluminal coronary angiography (PTCAI; elevated blood levels of triglycerides, of total cholesterol or of LDL cholesterol, arteriosclerosis, peripheral vascular disease, cerebral vascular disease and pulmonary hypertension, migraine, cardiomyopathy, etc. Not one compound -- let alone a genus of trillions of compounds, could possibly be effective against such disorders generally.

In order to determine if any particular claimed compound to be useful in the treatment of a disease characterized by high low density lipoprotein particles or cholesterol levels in the blood, first the compound needs to be synthesized, formulated into a suitable dosage form, and subjected to clinical trials with a number of fundamentally different diseases listed above or test the compounds in an assay known to be correlated to clinical efficacy of such treatment. This is a large degree of experimentation.

The direction concerning treating diseases found in the specification merely states applicant's intention to do so. Applicant describes formulation having a recommended dosage amount in the range of 0.05 to 20 mg/kg of body weight per day, however, since no therapeutic agent having the ability to increase LDL receptor expression has ever been used in the treatment

of all types diseases which are characterized by high low density lipoprotein particles or cholesterol levels in the blood, one skilled in the art would not find sufficient guidance regarding the dosage regimen required for each of these different diseases. The specification provides one test procedure with no correlation to the assorted diseases covered by the instant claim. Applicant neither asserted nor it is art-recognized that the only procedure provided in the specification is correlated to the clinical efficacy of all of the diseases instantly claimed.

There is no working example of treatment of any of the diseases encompassed by the claims. The nature of the invention is clinical treatment of diseases with therapeutic agents having ability to increase LDL receptor expression, which involves physiological activity. Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

MPEP § 2164.01(a) states that "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1562, 27

USPQ2d 1510, 1513 (Fed. Cir. 1993)". That conclusion is clearly justified here and undue experimentation will be required to practice the claimed invention.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1. Claims 1-2, 11, 18, 41, 61-62, 95, 98, 100, 102, 108, 109 and 111 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over

claims 1-3 and 6-8 of U.S. Patent No. 6,121,304. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims substantially overlap the compounds of the reference claims. The instant claims recite that R^2 is heteroaryl which includes a 5-indazole and 5-indole. The reference claims recite that R^2 is phenyl wherein substituents at the 3- and 4-positions together form a ring together and therefore, the R^2 in the reference claims includes 5-indazole and 5-indole. Further, instant claims 11, 18 and 98 include the species specifically claimed in claims 3 and 8 of the reference. The reference compounds are taught to be useful as pharmaceutical agents, see the claims in the reference. It would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the species of the genus taught by the reference, including those instantly claimed, because the skilled chemist would have had the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole i.e., as pharmaceutical agents. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole.

This rejection was made in previous office actions (see e.g., November 28, 2003) and applicant indicated that the rejection be held in abeyance until the subject matter is otherwise found allowable.

2. Claims 43-44, 54-60, 96, 101, 103 and 106-107 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 7, 10-15, 16-18, 25-30 and 31-32 of U.S. Patent No. 6,417,176. Although the conflicting claims are not

identical, they are not patentably distinct from each other because the instant claims substantially overlap the therapeutic methods of the reference claims. The instant claims recite a method of treating a disease characterized by abnormally high LDL particles or cholesterol levels in blood, administering a compound of formula I wherein R^2 is optionally substituted heteroaryl. The reference claims are also drawn to same method of treating administering a compound of formula (shown in claim 1 of the reference) wherein Ar is a pentafluorophenyl (see claim 3); and R^2 and R^3 together form a fused ring (see e.g., the compound in col. 12, lines 45-55). It would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the species of the genus taught by the reference, including those instantly claimed, because the skilled chemist would have had the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole i.e., as pharmaceutical agents. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole.

Allowable Subject Matter

Claim 3 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

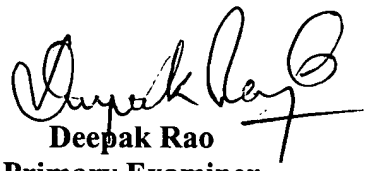
Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, Acting-SPE of 1624, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Deepak Rao
Primary Examiner
Art Unit 1624

September 30, 2005